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Nancy L. Stanisic
Center for Drug Evaluation and Research (HFD-1)
Food and Drug Administration
5600 Fishers Lane, rm. 9-64
Rockville, MD 20857
Sent via e-mail to staniscn@cder.fda.gov
cc: FDADockets@oc.fda.gov

RE: Docket No. 2005N-0038
Reporting of Adverse Events to Institutional Review Boards

Dear Ms. Stanisic,

Thank you for the opportunity to participate in the upcoming Food and Drug Administration (FDA) Public Hearing on the topic of Reporting of Adverse Events to Institutional Review Boards. My slide presentation is attached. I will be presenting on behalf of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI for which I served as the industry Co-Chairperson for four years. My participation in the CIOMS VI Working Group was sponsored by Wyeth Pharmaceuticals.

The Council provides a forum, under the auspices of the World Health Organization, for experts from government, industry and academia to come together in an unofficial capacity to discuss areas of mutual interest. The CIOMS Working Groups on drug safety have provided a mechanism for regulators and industry to develop proposals, with the hope that these proposals will eventually be adopted by national and regional regulators. Previous working groups have been successful in doing just that. For example, the recommendations of the CIOMS I Working Group led to the international harmonization of the criteria, timing and content of expedited reporting to regulatory authorities, including FDA.

As with previous working groups, the CIOMS VI Working Group included representatives from WHO, various regulatory authorities including FDA, pharmaceutical industry and research institutions. Among other covered topics, the CIOMS VI Working Group developed specific proposals for changes to the requirements for reporting adverse events and other safety information to institutional review boards (IRBs). The publication of the CIOMS VI Working Group recommendations, entitled "Management of Safety Information from Clinical Trials," is currently in press. The information most relevant to this discussion can be found in Chapter 7.

With the growing number of trials that are multinational and the expanding scope and size of the typical drug development program, what used to entail a couple of hundred subjects now often involves thousands or sometimes tens of thousands of subjects. The resulting increased volume of adverse event reports that investigators and IRBs must deal with can be staggering. While sponsors have become accustomed to reporting in an expedited fashion to regulatory authorities based on a well-established set of criteria, it is questionable whether it is useful to disseminate the same information to scores and sometimes hundreds of investigators and in turn to IRBs. Sponsors and regulatory authorities generally have computerized databases at their disposal for storing, cataloguing, coding and analyzing the information. Investigators and IRBs generally do not and are often overwhelmed with the amount of paperwork that comes their way. Even if the resources were available for each investigator to manage, maintain and analyze the data, the value of such redundancy is questionable. Likewise, while certain IRBs will continue to have the need to receive and review individual case reports from their own sites, they are ill-equipped to manage and interpret the many other case reports originating from other sites, often from other parts of the world, and to place them into proper perspective.

Unfortunately, while based on a well-intentioned desire to improve the protection of human subjects, the system has become a resource intensive activity that does not necessarily result in effective communication of useful safety information to those who need to know and act. The CIOMS VI Working Group believes that individual case reporting should not be considered synonymous with communication of important new safety information. When compliance is the goal, sponsors tend to err on the side of conservative assessments of causality and expectedness. In addition, it is well recognised that investigator assessment of causality is a crude and imprecise tool. As a result, individual case reports do not always (and often do not) include important new safety information. Conversely, important new information that is best derived from an overall analysis of reports in aggregate may not be effectively conveyed through sporadic case reporting.

Following, in italics, are the specific recommendations of the CIOMS VI Working Group.

The CIOMS VI Working Group recommends replacing the current practice of sending large numbers of individual case reports to investigators and ethics committees with a more reasonable approach to communicating important safety information to all who need to know. Such an approach would involve periodic and ad hoc *communications to investigators and ethics committees that include an update of important safety information as well as the evolving benefit-risk profile.*

For unapproved products, and in lieu of expedited reports, the CIOMS VI Working Group recommends periodic reports to investigators and IRBs that include a line listing of unblinded clinical trial cases that were expedited to regulatory authorities since the last periodic report, a copy of the current Development Core Safety Information (DCSI) along with an explanation of any changes, and a brief summary of the emerging safety profile. Although it is recommended that the default would be quarterly updates, there may be circumstances when a more immediate communication would be appropriate. Likewise, there may be circumstances when less frequent updates should be sufficient.

For approved products, the timeframe for periodic reports to investigators and IRBs would depend on the extent to which new indications are being developed. For a product undergoing Phase III trials, continuation of the quarterly reports would be advisable. For well-established products, less frequent updates would be appropriate and at some point, there should only be a need to update investigators and IRBs when there is significant new information to report.

When updates are provided by the sponsor to investigators or IRBs, whether for unapproved or approved products, line listings should include only unblinded expedited reports from clinical trials. The line listings should include interval data, i.e., only cases expedited since the last update; however, the summary of the emerging safety profile should take into account all of the accumulating data. The use of MedDRA preferred terms is recommended. The line listings generally should not include spontaneous reports; instead, significant issues arising from spontaneous reports can be described in narrative form in the update.

For Phase IV investigators and their associated IRBs, communication of changes to the Company Core Safety Information (CCSI) for the marketed product should be sufficient and periodic reports or line listings should no longer be necessary.

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor should issue a prompt notification to all parties, namely regulatory authorities, investigators and IRBs. A significant safety issue could be defined as one that has a significant impact on the course of the clinical trial or program (including the potential for suspension of the trial programme or amendments to protocols) or warrants immediate update of informed consent.

If these proposals are accepted and implemented through regulations, the CIOMS VI Working Group believes that the result will be a much more effective system for managing safety information from clinical trials, and more importantly, for identifying and communicating important new safety information to all who need to be informed and to take appropriate action in a timely manner.

Respectfully,

Wendy P. Stephenson, MD, MS, MPH